Outcomes of eosinophilic esophagitis in patients managed in a multidisciplinary clinic

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ABSTRACT

Background: *Eosinophilic esophagitis is a complex disease with an increasing prevalence. Multidisciplinary teams are often needed to manage this difficult-to-treat condition.*

Objective: *To observe the clinical and histologic outcomes of patients with eosinophilic esophagitis after management in a multidisciplinary clinic.*

Methods: *An observational, retrospective chart review was conducted to include all patients referred to the Walter Reed National Military Medical Center multidisciplinary eosinophilic esophagitis clinic between August 2012 and February 2021. Only patients who had at least one esophagogastroduodenoscopy before referral, one or more visits and endoscopy after multidisciplinary management, and documented clinical symptoms were included. Statistical analysis was performed by using McNemar and Wilcoxon tests.*

Results: *A total of 103 patients were included in the study, with a mean age at diagnosis of 17.9 years. Management in the multidisciplinary clinic was associated with a reduction in solid-food dysphagia by 70.9%, poor growth by 70.8%, and emesis or regurgitation by 87.5%. We observed that 48.5% and 62.1% had histologic remission (<15 eosinophils/hpf) on the initial and any post-multidisciplinary endoscopy, respectively. Only seven patients (5.8%) with two or more visits and endoscopies did not achieve histologic remission. More than two-thirds of the patients (68.9%) required combination therapy to achieve remission.*

Conclusion: *Although an observational study, these findings may suggest that the management of patients with eosinophilic esophagitis in a multidisciplinary clinic may improve the likelihood of clinical and histologic remission. Targeted management with a multidisciplinary approach may reduce overall morbidity and slow disease progression; however, more research is needed.*

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Eosinophilic esophagitis (EoE) is a chronic allergic esophagitis characterized by eosinophilic infiltration and inflammation in the esophagus that causes significant morbidity.[1,2] EoE is a lifelong disease that affects children and adults of all ages, which typically presents before the age of 50 years.[3] Presentation can vary based on the patient's age. Infants and toddlers typically present with failure to thrive and feeding difficulties, school-age children present with reflux symptoms unresponsive to conservative therapy, and adolescents and adults classically present with dysphagia.[3] In addition to physical morbidity, children and adolescents with EoE also have social and academic challenges, anxiety, depression, and sleep disturbances at significantly higher rates than does the general population.[4] With the increasing prevalence,[5] it becomes paramount to determine a management strategy that reduces morbidity and improves outcomes.

Despite the increasing prevalence of EoE, there remains a significant delay in the diagnosis of 6–12 years, given the nonspecific symptoms, especially in children.[6,7] This delay can have significant long-term consequences, including the development of strictures and, eventually, fibrosis.[6,7] Use of a a multidisciplinary approach is one strategy to expedite diagnosis, optimize management, and reduce morbidity. The diagnosis of EoE requires symptoms related to esophageal dysfunction, eosinophil (eos) predominant inflammation on esophageal biopsy specimen, with ≥ 15 eos/hpf, and exclusion of other causes that may be

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contributing to esophageal eosinophilia.[8] Additional historical clues, such as atopic conditions and endoscopic findings, to include esophageal rings, furrows, strictures, narrowing, and a positive tug sign[9] should increase the index of suspicion.[10]

Treatment remains a significant challenge for managing patients with EoE. In fact, there is no U.S. Food and Drug Administration approved medication for EoE.[11] The main goal of management is to improve clinical symptoms, histologic findings, and associated morbidity. A trial of proton-pump inhibitor (PPI) monotherapy is often the first step. Nonresponders are treated with a topical corticosteroid, elimination diet, or both. Elimination diets are also an effective treatment strategy when there is strict adherence. In some cases, a combination of these therapies is required to achieve clinical and histologic remission. Given that treatment plans are complex and individualized, active collaboration with an allergist, a gastroenterologist, and a dietician in a multidisciplinary clinic may lead to improved outcomes when compared with primary care or single subspecialty management.

A multidisciplinary approach allows multiple subspecialists to share knowledge and, ultimately, improve clinical outcomes.[12] Given the complexity of EoE management, it is recommended that these patients receive multidisciplinary care.[13–15] However, despite this recommendation, there remains a paucity of data that compared the patient outcomes before and after intervention. If improved outcomes when using a multidisciplinary approach are observed, then this may lead to a new standard of care that reduces the burden of health-care utilization and decreases morbidity. This observational study aimed to describe the clinical outcomes of a single-center multidisciplinary EoE clinic.

METHODS

In this single-center retrospective observational study, data were collected from patients enrolled in the multidisciplinary EoE clinic at Walter Reed National Military Medical Center (WRNMMC). Patient health records were accessed by using the electronic medical record and included demographic information (age at diagnosis and duration between diagnosis and referral to EoE clinic), atopic history, clinical symptoms, and esophageal biopsy results. Data were collected both before and after multidisciplinary EoE clinic management. This study was approved by the institutional review board at WRNMMC (WRNMMC-EDO-2020-0570).

All patients referred to the multidisciplinary EoE clinic between August 2012 and February 2021 were eligible for this study. Referral sources included the following: the allergy/immunology service and adult and pediatric gastroenterology services. During this period, 145 patients were evaluated in the multidisciplinary EoE clinic. Patients were included if they had been diagnosed with EoE per current consensus guidelines.[10] Patients also had to have one or more outpatient visits to the WRNMMC multidisciplinary EoE clinic, one or more outpatient visits to another clinical setting for management of EoE, one or more esophageal biopsy results both before and after EoE clinic visits, and documentation of symptoms on a follow-up visit to any outpatient clinic. A patient was excluded if the diagnosis of EoE was made without histologic evidence of esophageal eosinophilia (*i.e.*, <15 eos/hpf), an alternative diagnosis was made on further evaluation, or the patient received care outside of the multidisciplinary clinic at another treatment facility for their EoE.

Individualized treatment plans were reassessed and modified, if necessary, at each interval follow-up in the multidisciplinary clinic. Statistical analysis was performed by using IBM Statistical Product (International Business Machines (IBM), 1 New Orchard Road, Armonk, New York) and Service Solutions statistical software that compared pre– and post–multidisciplinary EoE clinic outcomes. Paired data analysis for binomial data was performed by using a nonparametric McNemar test. A Wilcoxon test was used to analyze nonparametric pre- and postintervention peak eos counts on esophagogastroduodenoscopy (EGD). Statistical significance was determined by $p \leq 0.05$.

RESULTS

Demographics

After applying inclusion and exclusion criteria, 103 patients enrolled in the multidisciplinary EoE clinic were included in the study population (Table 1). Fifty-seven were pediatric patients (55.3%) (0–18 years). Seventy-two patients (69.9%) were male. A history of atopy was observed in 82.5% of the patients, including 48.5% with two or more atopic conditions as follows: 63.1% with allergic rhinitis, 29.1% with atopic dermatitis, 44.7% with food allergy, and 19.4% with asthma. The mean age of diagnosis of EoE was 17.9 years (range, 1–63 years), with 50.5% being diagnosed at ≤ 11 years (40.8% of those were ages ≤ 5 years), and 14.6% were diagnosed after the age of 40 years. The mean duration from the diagnosis of EoE to referral to the multidisciplinary EoE clinic was 2.6 years (range, 0.08–30 years). Treatment modalities used before treatment in the multidisciplinary clinic are summarized in Table 1.

Clinical Outcomes

Before enrollment in the multidisciplinary EoE clinic, 53.4% of the patients had solid-food

Table 1 **Demographics of patients enrolled in the multidisciplinary EoE clinic**

	Pediatric Patients (*n* = 57)	Adult Patients (*n* = 46)	Overall (*N* = 103)
Sex, *n* (%)			
Male	41.0 (71.9)	31.0 (67.4)	72.0 (69.9)
Female	16.0 (28.1)	15.0 (32.6)	31.0 (30.1)
Age at diagnosis, median (min, max), y	3.00 (1.00, 17.0)	33.0 (13.0, 63.0)	11.0 (1.00, 63.0)
Time from diagnosis to EoE clinic visit, median (min, max), mo	1.00 (0.100, 7.00)	2.00 (0.0800, 30.0)	1.00 (0.0800, 30.0)
Diagnosis, *n* (%)			
Allergic rhinitis	33 (57.9)	32 (69.6)	65 (63.1)
Atopic dermatitis	27 (47.4)	3 (6.5)	30 (29.1)
Food allergy	34 (59.6)	12 (26.1)	46 (44.7)
Asthma	14 (24.6)	6 (13.0)	20 (19.4)
Strictures on pre-EoE EGD, *n* (%)	0 (0)	9 (19.6)	9 (8.7)
Pre-EoE treatment, *n* (%)			
Proton-pump inhibitor	24 (42.1)	37 (80.4)	61 (59.2)
Swallowed corticosteroid	23 (40.4)	20 (43.5)	43 (41.7)

EoE = Eosinophilic esophagitis; min = minimum; max = maximum; EGD = esophagogastroduodenoscopy.

Table 2 **Comparative clinical symptom outcomes between pre– and post–EoE multidisciplinary clinic**

	Pediatric Patients			Adult Patients			Overall		
		Post-Clinic			Post-Clinic			Post-Clinic	
Solid-food dysphagia									
		No	Yes		No	Yes		No	Yes
Pre-Clinic	No	36	1	No	11	0	No	47	1
	Yes	18	2	Yes	22	13	Yes	40	15
p		0.0002			<0.0001			<0.0001	
Poor weight gain									
		No	Yes		No	Yes		No	Yes
Pre-Clinic	No	33	0	No	46	0	No	79	0
	Yes	17	7	Yes	0	0	Yes	17	7
p		0.0001			—			0.0001	
Emesis and/or regurgitation									
		No	Yes		No	Yes		No	Yes
Pre-Clinic	No	24	0	No	31	0	No	55	0
	Yes	29	4	Yes	13	2	Yes	42	6
p		<0.0001			0.0009			<0.0001	

EoE = Eosinophilic esophagitis.

dysphagia, 23.3% had poor weight gain, 46.6% had emesis or regurgitation (Table 2), and 8.7% had strictures on EGD (Table 1). Adult patients more commonly presented with solid-food dysphagia (76.1%) compared with pediatric patients who more frequently had poor weight gain (42.1%) and emesis or regurgitation (59.6%). After management in the EoE clinic, only 15.5% ($p < 0.001$) of the patients had solid-food dysphagia, 6.8% had poor weight gain ($p = 0.001$), and 5.8% had emesis or regurgitation ($p < 0.001$), as summarized in Table 2. In those patients with symptoms and who did not not attain histologic remission during the study period, 30.4% continued to have solid-food dysphagia, 33.3% had weight difficulties, and 18.8% had emesis or regurgitation.

Table 3 **Histologic remission comparing pre-EoE clinic and post-EoE clinic EGDs**

	Remission on EGD, *n* (%)*#			Mean Peak eos/hpf on EGD§		
	Pediatric Patients (*n* = 57)	Adult Patients (*n* = 46)	Overall (*N* = 103)	Pediatric Patients (*n* = 57)	Adult Patients (*n* = 46)	Overall (*N* = 103)
Pre–EoE clinic EGD	11 (19.3)	1 (2.2)	12 (11.7)	44.2	57.0	49.9
First Post-EoE clinic EGD	30 (52.6)	20 (43.5)	50 (48.5)	23.5	32.5	27.5
p	<0.001	<0.001	< 0.001	<0.001	0.006	<0.001
Post-EoE clinic any EGD	43 (75.4)	21 (45.7)	64 (62.1)	—	—	—
p	<0.001	<0.001	<0.001	—	—	—

EoE = Eosinophilic esophagitis; eos = eosinophil; EGD = esophagogastroduodenoscopy.
**Remission is defined as < 15 eos/hpf.*
#The p values were determined by using the McNemar nonparametric test compared with remission on the pre–EoE clinic EGD.
§The p values were determined by using the Wilcoxon nonparametric test compared with peak eos/hpf on the EGD in the pre–EoE clinic.

Histologic Outcomes

In the study population, 35 patients had two or more EGDs, 20 had three or more EGDs, 12 had four or more EGDs, and 10 had five or more EGDs. The rates of histologic remission, defined as < 15 eos/hpf, were determined before and after EoE clinic. Twelve patients (11.7%) were in remission before management in the multidisciplinary EoE clinic (Table 3). Sixty-four patients (62.1%) achieved histologic remission during their management in the EoE clinic: 43 pediatric patients (75.4%) and 21 adults (45.7%). Fifty patients (48.5%) had < 15 eos/hpf after their first EGD. A statistically significant improvement was observed in remission outcomes at any time in all study groups (Table 3).

Treatment Outcomes

Both pre– and post–EoE clinic management involved single or combination therapy with a PPI, swallowed corticosteroid, and/or an elimination diet. Treatment duration in the multidisciplinary EoE clinic ranged from 0.5 to 8.5 years. In the pre–EoE clinic, 45 pediatric patients (78.9%) and 16 adults (34.8%) were treated with an elimination diet (single or combination therapy) compared with 50 pediatric patients (87.7%) and 21 adults (45.7%) in the post–EoE clinic. Importantly, 13 of 15 pediatric patients and 4 of 4 adult patients achieved remission on their first EGD post–EoE clinic visit when treated with an elemental diet. The two pediatric patients who did not achieve remission on the first EGD while on an elemental diet achieved it on the second EGD. Pediatric patients managed on any treatment modality had > 50% remission observed after the first EGD. The adults were generally more difficult to treat, with all treatment regimens achieving ≤ 50% rates of remission. Even when using a more stringent histologic remission criteria of ≤ 5 eos/hpf as used in interventional trials,[16] 53 patients (51.5%) achieved remission on one or more EGD during the study period. The remission rates on EGD for each treatment modality during the study period are summarized in Table 4.

DISCUSSION

EoE is a complex and difficult condition to manage and often requires the involvement of a multi-disciplinary approach to treat. However, despite the presence of multidisciplinary EoE clinics at some major hospital centers, to our knowledge, there has not been a large single-center study that evaluated their outcomes. This study evaluated 103 adult and pediatric patients with EoE over a period of nearly 9 years. The demographics of the patients included in this study were generally representative of patients with EoE in the United States (65% are male, 55.8% present with dysphagia, and the mean age of diagnosis is 33.5 years).[17] The younger patient age in this study population likely reflects a younger mean age of active-duty service members compared with the general population and the large sample of pediatric patients. In addition, in the United States, ~52.8% have at least one atopic condition, less than the 82.5% observed in this study.[17] The study population had a higher prevalence of atopic conditions likely given that the more complex and difficult-to-treat patients (*i.e.*, more atopic conditions) were those who were commonly referred to the multidisciplinary EoE clinic. The prevalence of comorbid EoE with allergic rhinitis is 41.8% and asthma is 23.4% in the United States compared with 63.1% and 19.4% in this study, respectively.[17] The higher prevalence of allergic rhinitis in this study may be due to the overall increasing prevalence of atopic conditions in

Table 4 **Pre–EoE and post–EoE clinic treatment modalities and remission outcomes**

Treatment	Pre–EoE Clinic Treatment, *n* (%)			Post–EoE Clinic Treatment, *n* (%)			Post–EoE Treatment / Remission, *n* (%)		
	Pediatric Patients (*n* = 57)	Adult Patients (*n* = 46)	Overall (*N* = 103)	Pediatric Patients (*n* = 57)	Adult Patients (*n* = 46)	Overall (*N* = 103)	Pediatric Patients (*n* = 43)	Adult Patients (*n* = 21)	Overall (*N* = 103)
None	3 (5.3)	3 (6.5)	6 (5.8)	0 (0)	0 (0)	0 (0)	—	—	—
PPI only	2 (3.5)	14 (30.4)	16 (15.5)	0 (0)	7 (15.2)	7 (6.8)	—	3 (14.3)	7 (6.8)
Swallowed corticosteroid only	4 (7.0)	1 (2.2)	5 (4.9)	3 (5.3)	9 (19.6)	12 (11.7)	2 (4.7)	4 (19.0)	12 (11.7)
Elimination diet only	19 (33.3)	3 (6.5)	22 (21.4)	8 (14.0)	6 (13.0)	14 (13.6)	5 (11.6)	3 (14.3)	14 (13.6)
PPI + swallowed corticosteroid	3 (5.3)	12 (26.1)	15 (14.6)	4 (7.0)	9 (19.6)	13 (12.6)	3 (7.0)	4 (19.0)	13 (12.6)
Swallowed corticosteroid + elimination diet	7 (12.3)	2 (4.3)	9 (8.7)	13 (22.8)	2 (4.3)	15 (14.6)	12 (27.9)	1 (4.8)	15 (14.6)
PPI + elimination diet	10 (17.5)	6 (13.0)	16 (15.5)	15 (26.3)	4 (8.7)	19 (18.4)	12 (27.9)	2 (9.5)	19 (18.4)
PPI + elimination diet + swallowed corticosteroid	9 (15.8)	5 (10.9)	14 (13.6)	14 (24.6)	9 (19.6)	23 (22.3)	9 (20.9)	4 (19.0)	23 (22.3)

EoE = Eosinophilic esophagitis; PPI = proton-pump inhibitor.

developed countries and potential selection bias given that one source of referrals was the allergy/immunology service.[18,19]

Notably, a statistically significant reduction in all the clinical symptoms for both pediatric and adult patients was observed. The prevalence of solid-food dysphagia decreased drastically, by 70.9%; poor growth by 70.8%; and emesis or regurgitation by 87.5%. The prevalence of strictures on EGD decreased by 88.9%. This was an important finding given that EoE is a progressive disease. Inadequate management can lead to worsening solid-food dysphagia and food impaction, which leads to increased morbidity, esophageal dilations, and emergency department visits.[20,21] A significant number of food impactions require endoscopy, and many children and adults have recurrent impaction.[21,22] A multidisciplinary EoE clinic allows for close follow-up and shared decision-making among subspecialists, which, according to this study, seemed to be associated with improved clinical outcomes.

Another important marker of disease management of EoE is the histopathologic findings. Symptom severity has been associated with peak intraepithelial–subepithelial eos counts on EGD.[23] Patients without subclinical remission (*i.e.,* ≥15 eos/hpf) are more likely to experience more-advanced disease progression to include rings, subepithelial fibrosis, microabscesses, basal layer hyperplasia, lymphoid follicles, and degranulation.[23] Those with elevated eos on EGD are at a higher likelihood of experiencing dysphagia and food impaction as both short- and long-term complications of EoE.[24] Before management in the multidisciplinary EoE clinic, only 12 of 103 patients (11.7%) met the criteria for histologic remission. These patients were referred to the EoE clinic primarily for comprehensive management in transitioning from medical therapy to an elimination diet. After the first EGD after treatment in the EoE clinic, 51.5% of the patients were in remission. Sixty-four patients (62.1%) had remission seen on at least one EGD during the study period. Of the remaining 39 patients (37.9%), only 7 who had regular follow-up (defined as two or more visits to the EoE clinic) did not achieve disease remission on EGD. Of those seven patients, one achieved remission outside of the study period, two were asymptomatic, and three were lost to follow-up. Importantly, given the above findings of higher rates of remission, multidisciplinary management may lead to fewer clinical symptoms, along with food impactions and thus fewer emergency department visits or hospitalizations.

Given the complexity in the treatment of EoE, management is often targeted to individual patients with a variety of therapies. This study observed similar findings. More than two-thirds of the patients (68.9%) required at least two treatment modalities to achieve clinical and/or histologic remission, which thus

highlighted the complexity of disease management in patients with EoE. Some therapies were observed to have higher rates of remission. Interestingly, pediatric patients had high rates of remission on all single and combination therapies used (single PPI therapy not used), with ≥ 60% achieving histologic remission. Adults, instead, had lower remission rates in all the treatment groups compared with pediatric patients. This may be secondary to a difference in medication and diet adherence rates, regular follow-up, and/or the presence of more-advanced disease.[25] Remission rates for adults in this study may have been lower for those who opted to transition from PPI or topical steroid to strict elimination diet. With transition to an elimination diet, management typically includes follow-up EGDs that often show worse histologic outcomes early on in treatment. However, comparative studies between adult and pediatric patients with EoE are needed to identify these differences.

This study had several important strengths. First, this unique, large, retrospective, cohort, single-center observational study included a population of 103 patients with EoE that was largely representative of the general population, which allowed its findings to be applied to other national hospital centers. Second, this study spanned nearly a decade, which ultimately allowed for close observation of both clinical and histologic outcomes over time. Another strength is that, over the study period, the patients in the EoE clinic were managed by the same allergist (CM) and gastroenterologist (SM) at a single center, which allowed for less variability in the treatment. Also, there was consistent follow-up with the patients given the universal insurance health-care coverage for this population, which thus allowed for decreased financial burden, which eliminated this confounding variable in data analysis of outcomes.

Several limitations also need to be addressed. First, given that this study involved nearly a decade of data, there is likely some error in both documentation and data collection. Another limitation was that the adherence of individual patients in their follow-up visits and treatment plans could have impacted the clinical and histologic outcomes, likely attributed to patients moving out of the area secondary to military service. A further limitation was that additional measures of disease control, such as endoscopic reference scores and pediatric EoE symptom scores, were not available. In addition, because this was a retrospective observational study, a determination of cause and effect could not be made.

CONCLUSION

This large, retrospective, observational study that involved > 100 patients from a single center demonstrated promising results in the impact of multidisciplinary management of EoE in reducing clinical symptoms and histologic outcomes. Importantly, this study was also before new treatments, such as dupilumab and other biologics, were introduced. Given that EoE is often a difficult disease to treat, we hope that this study will encourage other hospitals to enroll patients in a multidisciplinary clinic to help manage clinical symptoms and slow disease progression. When multidisciplinary EoE clinics are not readily accessible, close follow-up and shared decision-making will be important in managing these patients. As the understanding of EoE continues to evolve, more studies are needed to examine different treatments and their associations with clinical and histologic remission.

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